# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 20-011/S-021

## MEDICAL REVIEW(S)

NDA 20-011/s021
NDA 20-708/s011

# DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

## Medical Officer's Review of Efficacy Supplements

| | |
|---|---|
| **NDAs** | NDA 20-011/s021 and NDA 20-708/s011 |
| **Applicant** | TAP Pharmaceutical Products<br>675 North Field Drive<br>Lake Forrest, IL 60045 |
| **Submission Type** | Efficacy Supplement |
| **Drug** | |
| **Established name** | Leuprolide acetate for depot suspension |
| **Trade name** | Lupron Depot 3.75 mg (NDA 20-011)<br>Lupron Depot 3 Month 11.25 mg (NDA 20-708) |
| **Chemical class** | Synthetic peptide |
| **Chemical name** | 5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-proamide acetate salt |
| **Drug Class** | Gonadotropin releasing hormone (GnRH) agonist |
| **Indication** | Management of endometriosis |
| **Route of Administration** | Intramuscular injection |
| **Dosage Form** | Sterile depot suspension for injection |
| **Dose** | 3.75 mg or 11.25 mg per dosing |
| **Dosing Regimen** | Once a month (3.75 mg formulation) or<br>Once every 3 months (11.25 mg formulation) |
| **Dates** | |
| **Submitted** | November 21, 2000 |
| **CDER stamp date** | November 22, 2000 |
| **PDUFA date** | November 22, 2001 |
| **Related NDAs** | NDAs 19-010, 19-732, and 20-517 (prostate cancer); NDA 19-943 (uterine leiomyomata); NDA 20-263 (precocious puberty) |
| **Related IND** | [redacted] |
| **Medical Reviewer** | Scott Monroe MD |
| **Date Review Completed** | September 7, 2001 |

**FINAL**

21 September 2001

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## 3 INTRODUCTION AND BACKGROUND

### 3.1 Drug

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| • **Established Name** | Leuprolide acetate for depot suspension |
| • **Trade Name** | Lupron Depot 3.75 mg (NDA 20-011)<br>Lupron Depot 3 Month 11.25 mg (NDA 20-708) |
| • **Drug Class** | Gonadotropin releasing hormone (GnRH) agonist |
| • **Chemical Class** | Synthetic decapeptide |
| • **Chemical name** | 5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-proamide acetate salt |
| • **Indication** | Management of endometriosis |
| • **Dosage Form** | Sterile depot suspension for injection |
| • **Dose** | 3.75 mg or 11.25 mg per dosing |
| • **Dosing Regimen** | Once a month (3.75-mg formulation) or<br>Once every 3 months (11.25-mg formulation) |

### 3.2 Overview of Disease and Treatment Options

#### 3.2.1 Endometriosis

Endometriosis may be defined as the presence of functioning endometrial tissue outside of the uterus. It is usually confined to the pelvis in the region of the ovaries, uterosacral ligaments, cul-de-sac, and uterovesical peritoneum. It is a common gynecologic disorder that is present in up to 10% of reproductive-aged women. The most common symptom of endometriosis is pain that may include dysmenorrhea, chronic pelvic pain that is not associated with menses, and/or dyspareunia. Endometriosis is also frequently associated with infertility. The clinical presentation and severity of the symptoms of endometriosis are related to some degree to the anatomic location and the extent of the disease. However, some women with anatomically advanced disease may have few pain symptoms while other women with minimal anatomic disease may have severe and disabling symptoms. Although the etiology of endometriosis remains controversial, the disease is dependent on estrogen in most instances and is rarely seen after the menopause. Current therapies for endometriosis include analgesics, sex steroid hormones, agonistic analogs of gonadotropin releasing hormone (GnRH), and surgery. Hormonal therapies such as combination hormonal contraceptives, progestins (medroxyprogesterone acetate or norethindrone) or danazol may act both directly on the ectopic endometrial tissue and indirectly via a reduction in circulating levels of ovarian estrogens. In contrast, agonistic analogs of GnRH such as Lupron act only indirectly on the ectopic endometrium by inducing a hypoestrogenic state and reducing serum estradiol concentrations to postmenopausal levels in most women.

#### 3.2.2 GnRH Analogs for the Management of Endometriosis

Chronic administration of agonistic analogs of GnRH to women either by twice daily nasal spray (Synarel®), monthly or less frequent depot injection (Lupron Depot®), or implant (Zoladex®) initially stimulates and then suppresses the secretion of pituitary luteinizing hormone (LH), and to a

lesser degree, follicle stimulating hormone (FSH). These changes in LH and FSH secretion, in turn, initially stimulate the secretion of ovarian steroids. However, within 2 to 4 weeks of the onset of GnRH therapy, ovarian function is markedly reduced because of the absence of gonadotropin stimulation. In most women treated with approved doses of GnRH analogs, serum concentrations of estradiol are reliably suppressed to postmenopausal levels (i.e., ≤ 20 pg/mL).

The first GnRH analog to receive regulatory approval by the FDA for the management of endometriosis was nafarelin (Synarel®) in February 1990. This was followed by approvals for leuprolide (Lupron Depot® 3.75 mg under NDA 20-011) and goserelin (Zoladex®). Because of the side effects attributable to the hypoestrogenic environment induced by GnRH analogs, principally loss of bone mineral density [BMD]), the approved duration of treatment with GnRH agonists for the management of endometriosis is presently restricted to 6 months and retreatment is generally not recommended.

Symptomatic relief is usually noted during the first month of treatment with GnRH analogs and may continue for many months or even years after completion of 6 months of treatment. However, there are patients for whom retreatment is warranted because of recurrence of symptoms. Approaches to increasing the permissible duration of GnRH agonist treatment or to eliminating the recommendation against retreatment have investigated ways to limit the hypoestrogenic side effects, most importantly the loss of BMD. Co-treatment with a GnRH analog and sex-steroid hormones, referred to as "add-back" therapy, has been evaluated for its potential ability to minimize bone loss and to ameliorate vasomotor symptoms while preserving efficacy. Treatment protocols have included the addition of progestins alone and progestins plus estrogen. Other approaches have include co-administration of a GnRH analog and an anti-resorptive agent (e.g., a bisphosphonate).

## 3.3 Regulatory History of Lupron and Lupron plus Norethindrone Acetate

### 3.3.1 Background

In an effort to change the labeling for Lupron to permit primary treatment for up to 1 year as well as retreatment, TAP Pharmaceuticals initially conducted a randomized, blinded, 4-arm clinical trial (Study M92-878) in which women with endometriosis were treated with either Lupron Depot alone (LD, 3.75 mg every 28 days) or LD plus one of 3 daily add-back therapies for up to 1 year. The 3 add-back therapies were (1) 5 mg norethindrone acetate (NETA, Aygestin®) per day, (2) 5 mg NETA plus 0.625 mg conjugated equine estrogen (CEE), and (3) 5 mg NETA plus 1.25 mg CEE. All of the treatments were evaluated for their ability to ameliorate hypoestrogenic side effects while maintaining the efficacy of Lupron (i. e., reduction in the severity of endometriosis associated pain). The findings of Study M92-878 suggested that co-treatment with norethindrone acetate 5 mg per day, either alone or in combination with CEE, and Lupron reduced the incidence and severity of hot flashes and reduced the degree of bone loss as assessed by BMD measurements of the lumber spine. There were no clinically significant added benefits, however, from the inclusion of CEE above that provided by NETA alone. A numerically higher percentage of patients treated with LD plus NETA plus 1.25 mg CEE also terminated prematurely from the study. Based on the findings from this study, TAP submitted an efficacy supplement to NDA 20-011 in 1996 in order to change the labeling for Lupron to allow for treatment of women with endometriosis for up to 1 year as well as retreatment if NETA was co-administered with Lupron. The Division of Reproductive and Urologic Drug Products (DRUDP) refused to file the application because (1) it was based on a single study (M92-878) and (2) adequate dose ranging data were not provided for the add-back or hormone replacement therapies

for either a progestin alone or a progestin plus estrogen. However, TAP was allowed to add the following information to then current Lupron labeling:

> **"Changes in Bone Density:**
>
> A controlled study in endometriosis patients showed that vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. In this same study, LUPRON DEPOT 3.75 mg alone and LUPRON DEPOT 3.75 mg plus three different hormonal add-back regimens were compared for one year. All add-back groups demonstrated mean changes in bone mineral density of ≤ 1% from baseline and showed statistically significantly (P-value <0.001) less loss of bone density than the group treated with LUPRON DEPOT 3.75 mg alone, at all time points. Clinical studies suggest that the addition of hormonal replacement therapy (estrogen and/or progestin) to LUPRON is effective in reducing loss of bone mineral density which occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. The optimal drug/dose is not established."

DRUDP also requested that the Sponsor conduct a second study to confirm that add-back therapy reduced the degree of BMD loss resulting from 1 year of treatment with Lupron.

### 3.3.2 Subsequent Regulatory Interactions and Decisions

- TAP submitted a new clinical protocol (Study M97-777) to DRUDP in December 1997 to study the effects of 1 year of treatment with Lupron plus NETA (5 mg/day) on BMD and the signs and symptoms of endometriosis. The protocol was reviewed by DRUDP and a few suggestions, primarily statistical, were conveyed to the Sponsor. The Sponsor also was informed that a successful outcome, in terms of reducing or preventing bone loss, would be a change in BMD from baseline at 1 year of treatment of no greater than –2.2% (i.e., the lower bound of a 2-sided 95% CI of the difference from baseline could be no lower than -2.2%).
- The medical reviewer of the protocol did not comment upon the Sponsor's selection of 5 mg of NETA, without further supportive dose ranging data, as the only dose to be investigated.
- In July 2000, a teleconference was held with TAP to discuss the content of the revised efficacy supplement for NDA 20-011. Based on the information provided by TAP at that time, the Sponsor was told that they could proceed with submission of the efficacy supplement.
- In November 2000, TAP submitted efficacy supplements to NDA 20-011 (Lupron Depot 3.75 mg) and NDA 20-208 (Lupron Depot 3 Month 11.25 mg). The submission included the data from Study M92-878, the treatment phase of Study M97-777, proposed labeling, and literature references. Data from the 1-year posttreatment follow-up phase for Study M97-777 were not included. The objectives of the efficacy supplements were to make the following changes in the label for Lupron Depot 3.75 mg and Lupron Depot 3 Month 11.25 mg:

  1. To add information describing the beneficial effects of co-administration of 5 mg NETA with Lupron on reducing the hypoestrogenic adverse effects associated with Lupron treatment alone.
  2. To extend the allowable treatment period from 6 months to a maximum of 12 months if Lupron were co-administered with 5 mg NETA.
  3. To allow for retreatment if Lupron were co-administered with 5 mg NETA.

### 3.3.3 Regulatory and Clinical Background of Lupron Depot 3 Month 11.25 Mg

Both clinical studies submitted in support of the labeling changes requested in these applications were conducted with Lupron Depot 3.75 mg (LD) which is administered once monthly. No clinical data regarding co-treatment with Lupron Depot 11.25 mg (LD-3), which is administered once every 3 months, were submitted. The Sponsor stated that clinical findings obtained with Lupron Depot 3.75 mg also would be applicable to patients treated with Lupron Depot 11.25 mg plus NETA since the approval of the latter formulation in 1997 for the treatment of endometriosis was based on demonstrating pharmacodynamic "equivalence" to the monthly formulation. Pharmacodynamic equivalence of the 2 formulations was investigated in Study M94-139 in which 20 normal women received a single IM dose of Lupron 11.25 mg. Based on the serum concentrations of estradiol in these women, Lupron 11.25 mg was considered to be pharmacodynamically equivalent to the 1-month formulation and was approved for the treatment of endometriosis. At the time of approval, the Sponsor also was conducting a comparative clinical trial of Lupron 3.75 mg and Lupron 11.25 mg (Study M96-506) in women with endometriosis. Completion and timely submission of the data from Study M96-506 under a Phase IV commitment was a condition of approval for Lupron 11.25 mg under NDA 20-708.

Study M96-506 was a, 2 arm, open label study in which 41 women with endometriosis were randomly assigned to 6 months of treatment with either Lupron 3.75 mg (6 monthly injections) or Lupron 11.25 mg (two 3-month injections). The study included assessments of clinical efficacy (reduction in the painful symptoms of endometriosis), general safety, changes in bone mineral density (BMD), and pharmacokinetic/pharmacodynamic assessments (serum concentrations of leuprolide and estradiol). Based on his review of this study, the Medical Officer in DRUDP did not believe that there were any clinically significant differences between the 2 formulations in terms of efficacy or general safety. He also stated in his review that "there were no statistically significant differences in changes from baseline in estradiol levels between the Lupron 3.75 mg and Lupron 11.25 mg groups at any visit."

Bone mineral density of the lumbar spine (L1-L4) was to be measured at baseline, at the end of 6 months of treatment, and at 6-months posttreatment. The Medical Officer stated in his review that "there was a statistically significant mean percent change in BMD from baseline to the end of treatment noted for both the Lupron 3.75 mg and the Lupron 11.25 mg groups ... but there was not a statistically significant difference between the two treatment groups in the mean percent change in BMD from baseline values." The mean changes from baseline at the end of treatment (regardless of duration of treatment) according to the Medical Officer were –3.0% (LD group) and –2.8% (LD-3 group). In his review, the Medical Officer expressed some concern about the observed decreases in BMD in the Lupron 11.25 mg group because (1) BMD values had not returned to baseline values in many of the patients by the 6-month posttreatment assessment and (2) BMD values in 6 patients at the 6-month posttreatment assessment were numerically lower than those at the end of treatment. Five of these 6 patients had been treated with Lupron 11.25 mg.

**Medical Officer's Comment**

- *The magnitude of the BMD decreases from the end-of-treatment to 6-months posttreatment, however, did not exceed –1% in any of the patients, a change well within the error of the BMD measurements.*

The Sponsor's Interim and Final Reports for Study M96-506 included the BMD summary data listed in Table 4 below. In the Lupron 11.25 mg group, the mean percent decrease in BMD from baseline values was numerically less at the end-of-treatment and at 6-months posttreatment, but numerically greater at the final posttreatment assessment than in the Lupron 3.75 mg group.

**Table 4 Mean Percent Changes in Bone Mineral Density from Baseline (Study M96-506)**

| Assessment Time | Lupron Depot (3.75 mg) | | | Lupron Depot (11.25 mg) | |
|---|---|---|---|---|---|
| | N | Mean % change | | N | Mean % change |
| End of Treatment | 18 [1] | -3.0% | | 19 | -2.8% |
| 6-Months Posttreatment | 9 | -1.8% | | 14 | -1.5% |
| Any Time Posttreatment [2] | 14 | -1.6% | | 18 | -2.5% |

[1] Includes 2 patients treated for less than 3 months.

[2] Includes posttreatment BMD values obtained less than 6 months after completion of treatment.

Source: Final Study Reports for M96-506 (Treatment Phase and Posttreatment Phase Reports).

**Medical Officer's Comments**

- *Based on the data represented in Table 4, there is no suggestion that the decrease in BMD in patients treated with 2 doses of Lupron 11.25 mg (6 months of treatment) will be clinically significantly greater at the end of Treatment Month 6 or at 6-months posttreatment than that in patients receiving 6 monthly doses of Lupron 3.75 mg (the formulation used in the 2 clinical studies submitted in support of the efficacy supplements for NDA 20-011 and NDA 20-708).*
- *The numerically greater decrease in mean BMD in the Lupron 11.25 mg group at the "any time posttreatment" assessment is due to the inclusion of BMD values from 4 patients with end-of-treatment BMD decreases ranging from –2.3% to –7.3% whose posttreatment follow-up BMD assessments were obtained within 90 days of the end of treatment. Bone mineral density changes from baseline at the posttreatment follow-up visit in these 4 patients ranged from –2.2% to -9.5%. The period of time that had elapsed between the end-of-treatment and the posttreatment follow-up assessments in these patients was insufficient to permit maximal recovery of BMD.*
- *It has been shown in other studies with GnRH agonists that maximal BMD changes are often observed several months after the completion of treatment as the period of hypoestrogenemia may persist for several months after completion of the treatment period.*
- *Bone mineral density data submitted in the present application also indicate that recovery of BMD can continue through at least 1 year after completion of treatment with a GnRH agonist.*
- *In summary, the data submitted in support of the use of NETA to reduce Lupron-induced decreases in BMD (data obtained with the once monthly formulation) also should be applicable to patients treated with Lupron 11.25 administered once every 3 months for a period not to exceed 6 months (i.e. 2 doses) either as initial treatment or retreatment. This reviewer's recommendations concerning labeling changes therefore apply to both efficacy supplements submitted by the Sponsor.*

## 3.4 Other Relevant Information

### 3.4.1 Regulatory Status of Norethindrone Acetate (Aygestin®)

Norethindrone acetate (NETA) was approved by the FDA for marketing in 1982. It is available in 5 mg scored tablets. Present labeling states that Aygestin is indicated for the treatment of "secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence

of organic pathology." For the treatment of endometriosis the following dosage regimen is recommended per labeling:

> "Initial daily dosage of 5 mg Aygestin for two weeks. Dosage should be increased by 2.5 mg per day every two weeks until 15 mg of Aygestin is reached. Therapy may be held at this level for six to nine months or until annoying breakthrough bleeding demands temporary termination."

Contraindications to the use of Aygestin include the following:

1. Use in the first four months of pregnancy (this appears as a boxed warning).
2. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a history of these conditions.
3. Markedly impaired liver function or liver disease.
4. Known or suspected carcinoma of the breast.
5. Undiagnosed vaginal bleeding.
6. Missed abortion.
7. As a diagnostic test for pregnancy.

The following warnings and precautions are included in present labeling:

1. Discontinue medication pending examination if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine.
2. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

**Medical Officer's Comments**

- *Migraine headaches were reported in 7.3 and 19.1 percent of patients treated with Lupron plus NETA in Studies M92-878 and M97-777, respectively. Depression was reported in 14.5 and 25 percent of patients treated with Lupron plus NETA in Studies M92-878 and M97-777, respectively.*

### 3.4.2 Foreign Marketing Status of Lupron

Lupron Depot 3.75 mg as monotherapy is presently approved in most major markets for 6 months of treatment for the management of endometriosis. The Sponsor was asked to provide a list of markets and the relevant labeling where (1) treatment with Lupron is approved for a duration of greater than 6 months and (2) retreatment is approved. The Sponsor replied as follows:

> "One year of treatment for endometriosis was not approved in any countries without add-back. Add-back was approved in the Philippines (March 29, 2001) and Ireland (September 2000)."

In response to the question about retreatment, the Sponsor referred to labeling from Japan and Italy that was included in the Submission of August 10, 2001.

**Medical Officer's Comments**

- *Review of the approved drug labels for Japan and Italy, however, did not identify any specific references to retreatment.*

# 4 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

## 4.1 Toxicology Review

No preclinical toxicology data were submitted with these efficacy supplements.

## 4.2 Clinical Pharmacology and Biopharmaceutics Review

No significant new clinical pharmacology data, other than that related to suppression of serum estradiol concentrations, were submitted. These data were reviewed both by Dr. J. Lau in his Biopharmaceutics Review and briefly in the Efficacy Section of this review (see Section 8.5.3).

## 4.3 Chemistry Review

No significant new chemistry data were submitted with these efficacy supplements.

# 5 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

## 5.1 Pharmacokinetics

No pharmacokinetic data were submitted with these applications.

## 5.2 Pharmacodynamics

The effect of treatment with Lupron alone (LD) and Lupron plus norethindrone acetate (LD/N) on serum estradiol concentrations was assessed in the clinical studies submitted in support of these applications. These data are summarized briefly in the Efficacy Section of this review (see Section 8.5.3) and more thoroughly in the Biopharmaceutical Review.

# 6 DESCRIPTION OF CLINICAL DATA AND SOURCES

## 6.1 Clinical Data Submitted in Support of Efficacy Supplements

### 6.1.1 Clinical Trials

The clinical program supporting these efficacy supplements consisted of 2 multicenter studies (Study M92-878 and Study M97-777) in which women with painful symptoms of endometriosis were treated with Lupron Depot 3.75 mg either alone or in combination with hormonal add-back therapy. Both studies were conducted in the United States. Across the two studies, a total of 337 female patients with a diagnosis of endometriosis, confirmed by laparoscopy or laparotomy, were enrolled. Of these patients, 242 were treated with either Lupron alone or Lupron plus norethindrone acetate (NETA), the treatment regimens under review in this application. The remaining 95 patients were treated with Lupron plus NETA plus conjugated estrogens.

### 6.1.2 Secondary Sources of Clinical Data

A peer-reviewed, published communication summarizing the results of Study M92-878 was provided in the application (Hornstein M and et.: Leuprolide Acetate Depot and Hormonal Add-Back Therapy in Endometriosis: a 12-month Study, in Obstetrics and Gynecology 1998; 9116-24). The Sponsor also submitted several additional published communications (both original research and review articles) concerning co-treatment of women with endometriosis using a GnRH analog and a progestin and/or an estrogen.

## 6.2 Overview of Clinical Studies Included in the NDA

### 6.2.1 Study Objectives

Two clinical studies were submitted in support of this application (see Table 5 for an overview of the studies). The objectives of these studies were to evaluate the efficacy and safety of Lupron Depot 3.75 mg in combination with hormone add-back therapy (either 5 mg NETA alone or NETA plus estrogen) administered for one year for the management of endometriosis. The studies were designed and conducted to support a change in the labeling for Lupron Depot 3.75 mg and Lupron Depot 11.25 mg, reflecting the benefit of co-treating with Lupron plus NETA to extend the approved treatment period for endometriosis for up to one year and to permit retreatment.

The primary safety objective was to determine the degree of preservation of bone mineral density. Additional safety parameters included evaluation of adverse events and clinical laboratory measurements, particularly changes in serum lipid levels. Efficacy outcome measurements were secondary endpoints, and focused on improvement in the patient's painful symptoms and signs of endometriosis.

### 6.2.2 Clinical Studies

**Study M92-878**. This was a double blind, randomized, parallel group, multicenter study. Twenty-six (26) investigative sites participated in the conduct of the study. The study was conducted from November 1993 until December 1997. The objective was to determine the safety and efficacy of 1 year of treatment of women with endometriosis with (1) Lupron 3.75 mg alone or (2) Lupron in combination with (a) 5 mg norethindrone acetate (NETA) or (b) norethindrone acetate plus 1 of 2 doses of estrogen. Two hundred one (201) patients were enrolled and randomly assigned to 1 of the 4 treatment arms. Patients were followed for up to 24 months after completion of the 1 year Treatment Period.

**Study M97-777**. This was an open-label, single-arm, multicenter study. Twenty-four (24) investigative sites participated in the conduct of the study. The Treatment Period of the study was from February 1998 until March 2000. The objectives were (1) to evaluate the safety and efficacy of Lupron Depot 3.75 mg in combination with 5 mg norethindrone acetate administered for one year for the management of endometriosis and (2) to increase the number of women who were studied with this treatment regimen. One hundred thirty six (136) women were enrolled. Patients were followed for up to 12 months after completion of the Treatment Period.

**Table 5 Studies Supporting the Safety and Efficacy of Lupron 3.75 mg plus NETA**

| Study No. Study Title | Study Design | No. Sites Country | Number Of Patients and Treatment [2] | | | |
|---|---|---|---|---|---|---|
| | | | LD | LD+N | LD+N+ 0.625 CE | LD+N+ 1.25 CE |
| M92-878 Combination Lupron Depot – Hormonal Add-Back in the Management of Endometriosis | Double-blind, randomized, 4-arm, parallel-group, multicenter study with a 52-week Treatment Period and a 24-month Follow-up Period. | 26 US | 51 | 55 | 47 | 48 |
| M97-777 Combination Lupron Depot and Aygestin® Add-Back in the Management of Endometriosis [1] | Open-label, single arm, multicenter study with a 52-week Treatment Period and a 12-month Follow-up Period. | 24 US | | 136 | | |

[1] Aygestin = norethindrone acetate.
[2] LD = Lupron Depot 3.75 mg; LD+N = LD plus 5 mg norethindrone acetate; (3) LD+N+0.625 CE = LD + 5 mg N plus 0.625 mg conjugated equine estrogens (CEE); LD+N+1.25 CE = LD + 5 mg N + 1.25 mg CEE.
Source: Tables 10.1b of Final Report for Study M92-878 and 3.1b of the ISS.

# 7 CLINICAL REVIEW METHODS

## 7.1 Materials Submitted by the Sponsor

### Submissions to NDA 20-011(ES)

- Original efficacy supplement submitted on November 21, 2000. The supplement consisted of 26 paper volumes (narratives and primary statistical tables only) and data listings and case report forms (CRFs) in electronic format.
- First Safety and Efficacy Update submitted on March 21, 2001 (primarily an electronic submission).
- Second Safety and Efficacy Update submitted on June 20, 2001 (paper and electronic submission). This submission included all efficacy and safety data from the 1 year post treatment Follow-up phase of Study M97-777.
- Submission of August 10, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on July 26 and July 27, 2001.
- Submission of August 24, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on August 17, 2001.
- Submission of August 31, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on August 23, 2001.
- Submission of September 4, 2001. This submission was a response by the Sponsor to questions from the Medical Officer submitted on August 17, 2001 and August 30, 2001.
- Submission of September 12, 2001 containing requested serum prolactin levels in women with reported galactorrhea.

### Submissions to NDA 20-708 (ES)

- No original data or information specific to NDA 20-708, other than background information and revised labeling, was submitted. The application otherwise consisted entirely of cross-references to the materials submitted in support in NDA 20-011/s021.

## 7.2 Materials Reviewed and Overview of Review Procedures

### 7.2.1 Materials Reviewed

- All paper volumes included in the submission of November 21, 2000 (other than Volume No. 4 [CMC information]) as well as electronic data listing for adverse events, bone mineral density, laboratory safety data, and reasons for premature terminations were reviewed.
- Selected electronic CRFs were reviewed for clarification of safety or efficacy issues.
- All narratives and primary Statistical Tables in the Submission of June 20, 2001 (Final Safety Update) as well as associated data listings for adverse events, bone mineral density, laboratory safety data, and reasons for premature terminations were reviewed.
- A limited review of the information submitted on March 21, 2001 was conducted since all materials in this submission were included in the submission of June 20, 2001.
- All information in the Sponsor's responses to requests for additional information submitted August 10, 2001, August 24, 2001, August 31, 2001, September 4, 2001, and September 12, 2001 was reviewed.
- Interim and Final Reports for Study M96-506 and Medical Officer's Review of these reports.
- Medical Officer's Review of Original NDA 20-708 (Lupron Depot 11.25 mg).
- Medical Officer's Reviews of NDA 20-011/s012 (request to change labeling for Lupron Depot to allow treatment for up to 1 year that was not accepted for filing) and NDA 20-011/s014 (request to add information about hormone add-back therapy to label).
- Minutes of regulatory meetings and telephone conferences with Sponsor that were contained in Division Files regarding hormone "add-back therapy" in women receiving Lupron for the treatment of endometriosis.
- Publications submitted by the Sponsor that were included in the Submission of November 21, 2000.
- Publications known to the reviewer based on ongoing review of the medical literature in the area of medical treatment of endometriosis and the effects of GnRH treatment for endometriosis on bone mineral density.

### 7.2.2 Safety Updates

The sponsor submitted interim and final Safety Updates on March 21, 2001 and June 20, 2001. The final update contained all safety data obtained during the 1 year posttreatment Follow-up Period for Study M97-777. Information contained in the final Safety Update is included in the body of this review in Sections 9.4.6 (serious adverse events), 9.6.4 (posttreatment recovery of BMD), and 9.9.3.3 (serum lipids in the posttreatment period). These data were considered in the Medical Officer's final recommendations regarding the safety and efficacy of the Sponsor's applications.

### 7.2.3 Overview of Review Procedures

All narrative material provided by the Sponsor and primary statistical tables were reviewed by the Medical Officer. In addition, the Medical Officer prepared listings for safety laboratory data, bone mineral density measurements, and adverse events based on electronic files provided by the Sponsor.

When additional information or clarification was required, electronic CRFs were reviewed. If additional information was still required, queries were submitted to the Sponsor.

The accuracy of the Sponsor's primary efficacy analyses (reduction in painful symptoms of endometriosis) and primary safety analyses (changes in bone mineral density) were reviewed and confirmed by Kate Meaker MS, FDA statistician. Ms. Meaker's review did not identify any issues that would invalidate the Sponsor's analyses.

## 7.3 Overview of Methods Used to Evaluate and Ensure Data Quality

**DSI audits.** The primary objective and endpoint of the studies, namely, change in bone mineral density, was monitored and reviewed by an independent organization ——— Consequently, it was decided that DSI audits of specific investigative sites would not be necessary for this efficacy supplement.

**Financial disclosure statements.** Information concerning financial conflicts of interest was reviewed by Ms. Jeanine Best, Regulatory Project Manager, DRUDP. Her conclusion was as follows: "Adequate documentation was submitted to comply with 21 CFR 54. While the Sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. There was no disclosure of financial interests that could bias the outcome of the trials." The Medical Officer concurs with Ms. Best's assessment that there were no financial disclosures that would suggest the overall outcomes of either Study M92-878 or M97-777 was biased.

**Site monitoring.** According to the Sponsor the investigative sites were visited by a TAP Pharmaceutical Products Inc. study monitor at the start of the study. All sites were initiated and monitored regularly by a CRO ———— [Study M97-777]). Selected sites also underwent external quality assurance audits.

**Laboratory Assessments.** Serum chemistry and hematology measurements were performed centrally at ———— for Study M92-878 and at ———— for Study M97-777. Serum estradiol levels for Study M97-777 were measured at ————

**BMD measurements.** According to the Sponsor, bone mineral density measurements were performed by ——— trained technicians utilizing DEXA technology and Quantitative Digital Radiography machines (QDR). All DEXA scans were reviewed by ——— (currently known as ———— ) prior to electronic transmission of data to the Sponsor.

**Data entry.** According to the Sponsor, data entry into the computer database utilized in the analyses for the Study Reports included in this submission was performed using a procedure of double-entry of case report form and hormone data. The bone mineral density data file received from ———— and the clinical laboratory data file received from ———— were electronically loaded into the database.

**Medical Officer's Comments**

- *The ———— utilized by the Sponsor are well known laboratories that are often used by pharmaceutical companies for laboratory safety or endocrine measurements.*
- *DEXA is the current standard methodology for measuring BMD. ——— is the manufacturer of the QDR imaging machines that were used to measure BMD. ——— QDR machines are widely used both in clinical practice and in clinical trials.*

# 8 INTEGRATED REVIEW OF EFFICACY (PRINCIPAL CLINICAL STUDIES)

## 8.1 Efficacy Assessments

Although the 2 clinical studies submitted in support of this application differed significantly in terms of overall designs, the efficacy and safety assessments and endpoints of the 2 studies were very similar. Consequently, the studies are presented and evaluated in an integrated review. Since the Sponsor is seeking a labeling change concerning only the co-administration of Lupron plus NETA, this review will not discuss the findings in the NETA plus estrogen treatment arms in Study M92-878.

### 8.1.1 Primary Efficacy Assessments and Endpoints

**Clinical Assessment of Pain.** The primary efficacy variables in each study were based on the Investigator's and/or patient's assessment of the severity of each of 5 symptoms or signs of endometriosis. The disease variables that were assessed were dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and pelvic induration. Dysmenorrhea, pelvic pain, and deep dyspareunia were rated by the study coordinator after questioning the patient. Pelvic tenderness and pelvic induration were assessed by the investigator by performing a pelvic examination. Each symptom or sign was rated at each visit during the Treatment Period and at each visit during the first year of follow-up based on the grading scales listed in Table 6. Each symptom or sign was assigned a numeric score, based on its severity, of either 1 (not present); 2 (mild); 3 (moderate); or 4 (severe) for the purpose of analyses. This numeric scores were referred to as the "clinical symptom severity scores."

**Table 6 Grading of Symptoms and Signs of Endometriosis [1]**

| Symptom | Grade | Descriptor |
|---|---|---|
| Dysmenorrhea | Mild<br>Moderate<br>Severe | Some loss of work efficiency<br>In bed part of day, occasional loss of work<br>In bed 1 or more days – Incapacitation |
| Pelvic Pain | Mild<br>Moderate<br>Severe | Occasional pelvic discomfort<br>Noticeable discomfort for most of cycle<br>Requires strong analgesics [2]<br>Persistent during cycle other than during menstruation |
| Deep Dyspareunia | Mild<br>Moderate<br>Severe | Tolerated discomfort<br>Intercourse painful to the point of causing interdiction<br>Avoids intercourse because of pain. |
| Pelvic Tenderness | Mild<br>Moderate<br>Severe | Minimal tenderness on palpation<br>Extensive tenderness on palpation<br>Unable to palpate because of tenderness |
| Pelvic Induration | Mild<br>Moderate<br>Severe | Uterus freely mobile, induration in the cul-de-sac<br>Thickened and indurated adnexa and cul-de-sac, restricted uterine mobility<br>Nodular adnexa and cul-de-sac, uterus frequently frozen |

[1] Clinical grading scale of Biberoglu and Behrman. From Biberoglu KO and Behrman SJ, Dosage aspects of danazol therapy in endometriosis: Short-term and long-term effectiveness. Am J Obstet Gynecol, 139:645, 1981.
[2] Any narcotic analgesic.

The primary efficacy endpoints were the improvement from baseline for each of the 5 symptoms or signs of endometriosis. Clinical improvement (i.e., reduction in pain or induration) was expressed in terms of (1) the mean change in the symptom severity scores from baseline to the time of the assessment and (2) the proportion of patients who had complete resolution of the symptom or sign at the time of the assessment. (See Section 8.1.4 for an overview of the statistical analyses.)

### 8.1.2 Rationale for Efficacy Endpoints

The Biberoglu and Behrman grading scale is widely used to assess the severity of pain associated with endometriosis in clinical trials. This scale (or a modification) was used in the original NDAs for Lupron and the other GnRH analogs presently approved for the management of endometriosis.

**Medical Officer's Comment**

- *The primary efficacy assessments were referred to as the "clinical assessment of pain" by the Sponsor. This terminology (although not entirely accurate because the assessment of pelvic induration is not pain-based) will also be used in this review. A secondary efficacy assessment, based on the patient's completing a 10 point analogue pain scale, was referred to as the "patient assessment of pain" by the Sponsor (see Section 8.1.3 below).*

### 8.1.3 Secondary Efficacy Assessments and Endpoints

Secondary efficacy assessments and endpoints in both studies were:

- **Serum estradiol concentrations.** Serum estradiol concentrations were measured at 28 day intervals to determine if treatment with Study Drugs had suppressed estradiol to values similar to those observed in post menopausal women (i.e., ≤ 20 pg/mL).
- **Menstrual bleeding pattern.** Patients recorded in a daily diary whether they had menstrual bleeding. Based on these data, the proportion of women who had cessation of menstrual bleeding during treatment (i.e., developed amenorrhea) was determined for each treatment group.
- **Patient assessment of pain.** Patients assessed the severity of their symptoms of dysmenorrhea, pelvic pain, and deep dyspareunia on a 10 point analogue scales (0 = not present, 10 = intolerable). Based on these data, changes in the "patient's assessment of pain" during and following treatment with Study Drug was assessed.

### 8.1.4 Overview of Statistical Analyses for Primary Efficacy Endpoints

For each of the 5 clinical pain variables, the effects of treatment were analyzed and presented in several ways. These included the following:

1. The numerical change from the baseline value for the severity score at each on-treatment clinical visit.
2. The average numerical change from the baseline value, based on the severity scores at each clinical visit, during the treatment period.
3. The percentage of patients with the painful symptom or sign at baseline and at each clinical visit during treatment.

Further details concerning the primary and secondary efficacy analyses are presented in the separate statistical review prepared by the FDA statistician (Ms. K. Meaker).

**Medical Officer's Comments**

- *Based on the severity grading scale used by the Sponsor, the mean score for each of the 5 pain categories could range from 1 (all patients reported that the painful symptom was not present) to 4 (all patients reported severe or incapacitating pain for that symptom).*
- *According to the Sponsor, the planned sample size of 50 patients per treatment group would ensure 80% power to detect (at the 0.05 significance level, using two-sided tests and assuming a standard deviation of 0.9 severity levels) a difference in the reduction of pelvic pain between the Lupron-alone group and any add-back plus Lupron of 0.51 severity levels.*

## 8.2 Principal Clinical Trials to Support Efficacy Claim

### 8.2.1 Overall Study Design

**Study M92-878**. This was a double-blind, randomized, parallel group, multicenter study. Twenty-six (26) investigative sites participated in the conduct of the study. The study was conducted from November 1993 until December 1997. Two hundred one (201) patients with symptomatic endometriosis were enrolled and randomly assigned in a 1:1:1:1 ratio to treatment with 1 of 4 Study Drugs for up to 1 year. The 4 treatment arms were (1) Lupron 3.75 mg alone or (2) Lupron 3.75 mg in combination with either (a) 5 mg norethindrone acetate or (b) 5 mg norethindrone acetate plus 1 of 2 doses of estrogen. Patients were followed for up to 24 months after completion of the Treatment Period. The primary objective of this study was to investigate the efficacy and safety (e.g., preservation of BMD) of each of the 3 add-back regimens compared to treatment with Lupron alone.

**Study M97-777**. This was an open-label, single-arm, multicenter study. Twenty-four (24) investigative sites participated in the conduct of the study. The Treatment Period of the study was from February 1998 until March 2000. One hundred thirty six (136) women with symptomatic endometriosis were enrolled and treated for up to 1 year with Lupron 3.75 mg in combination with 5 mg norethindrone acetate. Patients were followed for up to 12 months after completion of the Treatment Period. The primary objective of this study was to increase the number of women who were treated with Lupron plus NETA to assess further the safety and efficacy of this treatment regimen.

### 8.2.2 Patients

Both Study M92-878 and Study M97-777 enrolled women with painful symptoms of endometriosis. The studies were designed to have similar patient selection criteria. Patients were considered for inclusion in the Studies if they met the following criteria.

#### 8.2.2.1 Inclusion Criteria

1. Patients were females between 18 and 40 years of age, inclusive.
2. Patients had a history of regular menstrual periods (three or more consecutive days of bleeding requiring protection) with cycle lengths of 21–35 days for at least three months prior to study enrollment.
3. Patients had a diagnosis of endometriosis established and staged (American Fertility Society [AFS] classification) at the time of laparoscopy or laparotomy, which was performed within 12 months prior to study entry.

4. Patients had pain in at least one of the following categories:
   - moderate or severe pelvic pain (not related to menstruation), or
   - moderate or severe deep dyspareunia accompanied by non-menstrual pelvic pain, or
   - moderate or severe dysmenorrhea accompanied by non-menstrual pelvic pain.
5. If patients had surgical reduction of endometriosis performed and/or received medical therapy for endometriosis, patients must have experienced persistence or recurrence of the same symptoms (as were present prior to either treatment) 3 or more months after completion of the treatment, and prior to study enrollment.
6. Patients must have had a negative result for a pregnancy test performed within one week prior to study entry. Unless patients had been surgically sterilized, they were required to agree to begin use of at least one form of barrier contraception during the pre-study period and to continue use throughout the entire Treatment Period and until onset of the first post-treatment normal menstrual period.

Differences in inclusion criteria were minimal, with Study M97-777 specifying that pre-study laboratory values had to be within 15% above or below the normal range unless considered by the Investigator to be within the limits of clinical acceptability and approved by the Sponsor.

Patients were excluded from participation if they met any of the following criteria.

#### 8.2.2.2 Exclusion Criteria

1. Patients with a hysterectomy and/or bilateral oophorectomy.
2. Patients whose surgical findings (i.e., evidence of endometriosis) were limited to adhesions or endometriomas.
3. Patients with prior therapy for endometriosis who had not met the minimum required washout period (6 months for GnRH analogs and 3 months for all other treatments). A minimum of 3 normal menses after cessation of prior therapy was required prior to the first dose of study drug.
4. Patients who were pregnant or had been pregnant within 3 months prior to the first dose of study drug.
5. Mothers who were still nursing.
6. Patients with undiagnosed abnormal genital/vaginal bleeding.
7. Patients with a history of thrombophlebitis or thromboembolic disorders.
8. Patients with cerebrovascular or coronary artery disease.
9. Patients with a calcium metabolism disorder, including urinary tract stone disease.
10. Patients with osteoporosis or other metabolic bone disease, or a bone mineral density of less than 80% of the age-matched control value.
11. Patients with a history of emotional disorder which precluded treatment with GnRH analogs.
12. Patients concurrently participating in another investigational study or who had received an investigational drug within one month prior to the first dose of study drug.
13. Patients with a history of hypersensitivity to previous hormonal therapy to which they might be exposed in the study.

Differences in exclusion criteria between the studies were limited to criteria about concurrent cancer. Study M92-878 excluded patients with known or suspected estrogen-dependent carcinomas (e.g., breast and endometrium). Study M97-777 had broader criteria, excluding patients with known or suspected cancer (other than basal or squamous cell cancer of the skin) that had not been in remission for five or more years prior to the first dose of study drug or who had received any systemic cancer chemotherapy within five years prior to the first dose of study drug.

Patients who had participated in Study M92-878 were precluded from participation in Study M97-777.

## 8.3 Study Drugs

### 8.3.1 Primary Study Drugs

**Study M92-878**. This was a 4 arm study in which patients were randomly assigned to 1 of 4 treatment groups.

- Group 1. Lupron Depot 3.75 mg (LD) alone
- Group 2. LD plus 5 mg norethindrone acetate (NETA, Aygestin®)
- Group 3. LD plus 5 mg NETA plus 0.625 mg conjugated equine estrogens (CEE, Premarin®)
- Group 4. LD plus 5 mg NETA plus 1.25 mg CEE.

Patients were randomly assigned in a 1:1:1:1 ratio to 1 of the 4 treatment groups.

**Study M97-777**. This was a single arm study in which all patients were treated with Lupron Depot 3.75 mg plus 5 mg NETA.

In both studies, patients were treated for up to 1 year (52 weeks).

### 8.3.2 Supplemental Study Drugs

In both studies, patients received supplemental calcium. In Study M92-878, calcium was provided as OsCal (500 mg elemental calcium [1250 mg calcium carbonate] per tablet). In Study M97-777, calcium was provided as OsCal 500 + vitamin D (500 mg elemental calcium and 125 mg vitamin D) per tablet. Patients were instructed to take 2 tablets daily.

### 8.3.3 Dosing Schedule

The initial Lupron Depot injection was to be administered between days 1-4 of the first menstrual cycle following the pre-study visit. Patients were to receive an IM dose of Lupron Depot 3.75 mg every 28 days. Patients who completed the treatment phase of the study received a total of thirteen injections of LD (52 weeks). Add-back therapy, or its corresponding placebo, was self-administered by the patients as one capsule daily. All patients were instructed to self-administer one calcium tablet twice each day. Patients were to continue taking calcium supplementation throughout the Treatment and Follow-up Periods.

### 8.3.4 Rationale for Dose Selection

In both studies the dose of Lupron Depot administered was the marketed and approved dose for the treatment of endometriosis.

**Study M92-878.** Norethindrone acetate 5 mg was selected based on previous research publications by academic investigators. These publications were based on limited exploratory studies that indicated that doses of norethindrone or norethindrone acetate in the range of 1.2 mg to 10 mg per day

could attenuated the decrease in bone mineral density that was associated with GnRH treatment of endometriosis. Conjugated equine estrogens 0.625 mg and CEE 1.25 mg were standard dosages used in estrogen replacement therapy at the time of study initiation for treatment of vasomotor symptoms and prevention of osteoporosis.

**Study M97-777.** Norethindrone acetate 5 mg was selected to confirm the results obtained in the NETA 5 mg treatment arm in Study M92-878.

**Medical Officer's Comments**

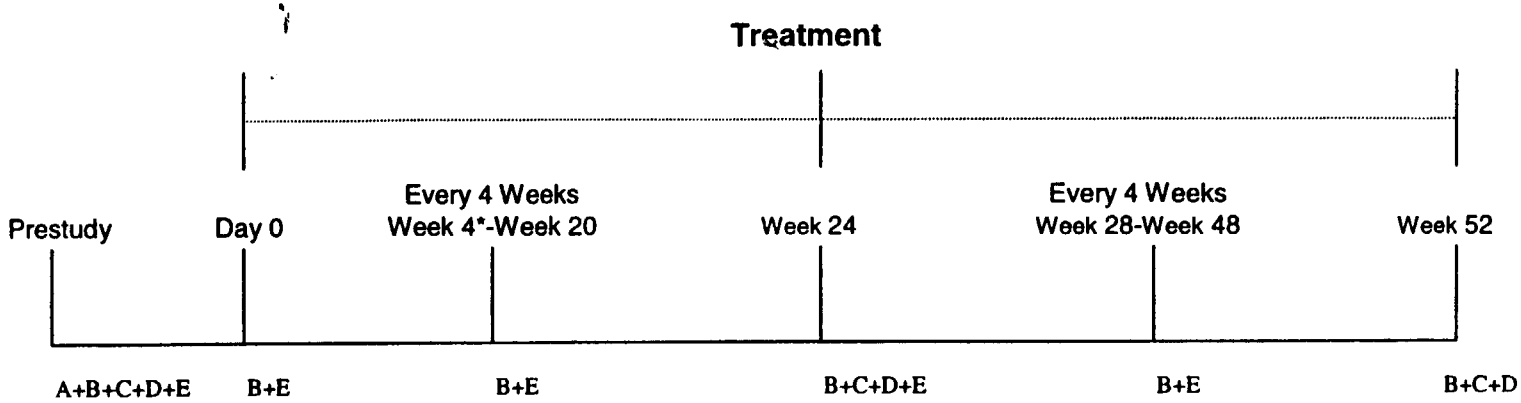
- *Studies cited by the Sponsor did not exclude the possibility that a daily dose of 2.5 mg of NETA would provide substantial protection against loss of BMD during treatment with Lupron with less adverse effects on lipid profiles (see Section 9.9.3).*
- *The Sponsor stated that the 2.5 mg dose was not investigated because a 2.5 mg dosage form of NETA is not presently marketed in the US. However, the 5 mg tablet that was investigated in the 2 clinical trials is scored, and thus a 2.5 mg dose could have been investigated.*

## 8.4 Study Conduct and Assessments

### 8.4.1 Schedule of Screening and Assessments

During the screening period, the patient's eligibility for the study was determined according to the inclusion and exclusion criteria described in Section 8.2.2). Laboratory procedures performed during screening included measurements of lumbar bone mineral density (BMD), serum chemistries, and hematology parameters. After the first injection of Study Drug on Day 0 (also referred to Day 1 in some data listings), patients were to return to the Study Center every 28 days for clinical and laboratory assessments and dosing with Lupron according to the schedule presented in Figure 1. After completion of the 1 year Treatment Period, subjects entered into a 12 month (Study M97-777) or 24 month (Study 92-878) posttreatment monitoring period in accordance with the schedule presented in Figure 2.

## Figure 1 Overview of Study Procedures (Treatment Period)




Start Barrier Contraception, Prestudy

A. Surgical Diagnosis Of Endometriosis
Pregnancy Test
Endometriosis History
Fertility History
Medical History
Menstrual History
Informed Consent

B. Clinical Evaluation
-Symptoms
-Pelvic Examination
Patient Pain Evaluation
Blood Draw for E2
Menstrual Record/Daily Log
Adverse Events
Concomitant Medications
Vasomotor Symptoms **

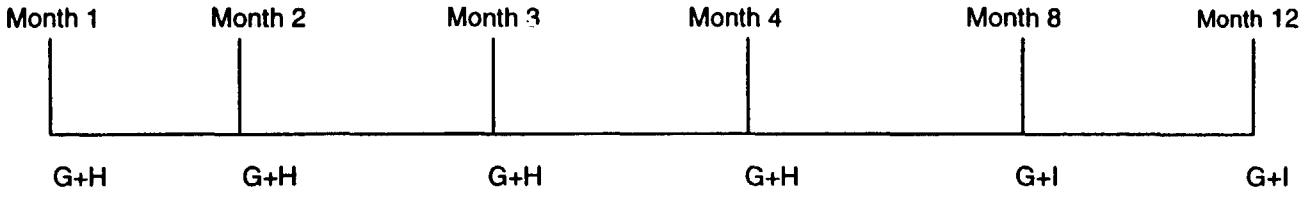
C. Bone Mineral Density

D. Physical Examination
Clinical Laboratory

E. Injection of Lupron

* At Week 4 only. Urine pregnancy test should be collected prior to dosing to confirm patient is not pregnant.
** Study M92-878 only.

## Figure 2 Overview of Study Procedures (Post-Treatment Period)




G. Clinical Evaluation *
-Symptoms
-Pelvic Examination
Patient Pain Evaluation
Blood Draw For Lipid Profile **
Menstrual Record/Daily Log
Adverse Events
Concomitant Medications

H. Blood Draw For E2
(After First Cycle Only)

I. Bone Mineral Density *

* A small number of patients in M92-878 were also monitored at Months 16, 20, and 24 for serum lipids, adverse events, and bone mineral density.

** In Study M92-878, posttreatment lipids were not collected prior to posttreatment Month 8.

### 8.4.2 Efficacy Assessments

The times at which the primary efficacy assessment (clinical evaluation of pain) and the secondary efficacy assessments (serum estradiol levels, menstrual suppression, and patient evaluations of pain) were to be performed are listed in Table 7 below.

**Table 7 Summary of Efficacy Evaluation Schedule**

| Efficacy Evaluation | Treatment Period | Follow-up Period |
|---|---|---|
| Clinical Evaluation of Pain | Day 0 and every 4 weeks through Week 52 | Every month through Month 4, then at Months 8 and 12 |
| Serum Estradiol Levels | Day 0 and every 4 weeks through Week 52 | Follow-up data considered safety data and not included in efficacy |
| Menstrual Suppression | Day 0, daily recording in patient diaries and summarized at each 4-week visit | Follow-up data considered safety data and not included in efficacy |
| Patient Evaluation of Pain | Day 0 and every 4 weeks through Week 52 | Every month through Month 4, then at Months 8 and 12 |

### 8.4.3 Pharmacokinetic Assessments

No pharmacokinetic data were collected in these clinical trials

## 8.5 Results

Since the Sponsor is not pursing a claim for treatment with Lupron plus NETA and estrogen, the remainder of this review will focus on the clinical findings from Lupron alone and the Lupron plus NETA treatment groups in Study M92-878 and the single treatment arm (Lupron plus NETA) in Study M97-777.

### 8.5.1 Study Population and Disposition of Subjects

#### 8.5.1.1 Demographics and Baseline Disease Characteristics

A total of 201 and 136 patients were enrolled into Studies M92-878 and M97-777, respectively. Of these 337 patients, 242 patients were randomized to treatment with either Lupron alone (51 patients in study M92-878) or Lupron plus NETA (55 patients in Study M92-878 and 136 patients in Study M97-777) and 95 patients were randomized to treatment with Lupron + NETA plus conjugated estrogens. The baseline demographic characteristics of the 242 patients randomized to treatment with Lupron or Lupron plus NETA are summarized in Table 8. There were no statistically significant differences between the 3 treatment groups with respect to age, height, or weight. The ages of the patients across the 3 treatment groups ranged from 17 to 43 years. The mean ages of the patients in each treatment group were very similar, ranging from 28.4 to 28.8 years. Although the weight of individual patients ranged widely, from 88 to 286 pounds, the mean weights of the 3 treatment groups were similar and ranged from 145.4 to 150.9 pounds. The majority of patients in the 2 clinical trials were Caucasian (211 of 242 [87%]). There was, however, a greater percentage of Black patients in the LD group (18%) than in either of the Lupron + NETA groups (5% and 10% in Studies M92-878 and M97-777, respectively). The difference between the distribution of races in the LD group in Study M92-878 and the LD/N group in Study M97-777 was statistically significant.

**Table 8 Baseline Demographic Characteristics**

| Parameter | | Study M92-878 LD N=51 | | Study M92-878 LD/N N=55 | | Study M97-777 LD/N N=136 | |
|---|---|---|---|---|---|---|---|
| Age (yrs) | Mean | 28.4 | | 28.7 | | 28.8 | |
| | Range | | | | | | |
| Height (in) | Mean | 65.0 | | 64.7 | | 64.6 | |
| | Range | | | | | | |
| Weight (lbs) | Mean | 145.4 | | 147.3 | | 150.9 | |
| | Range | | | | | | |
| Race [•] | | N | (%) | N | (%) | N | (%) |
| Caucasian | | 39 | (76) | 50 | (91) | 122 | (90) |
| Black | | 9 | (18) | 3 | (5) | 13 | (10) |
| Hispanic | | 3 | (6) | 2 | (4) | 0 | (0) |
| Oriental | | 0 | (0) | 0 | (0) | 1 | (1) |

[•] Statistically significant difference between groups (LD/N [Study M97-777] vs. LD [Study M92-878]; $p < 0.05$).
Source: Text Table 3.2a, pg. 53 (ISS).

Time to diagnosis of endometriosis, prior pregnancies, prior treatment for endometriosis, prior GnRH analog usage, and mean baseline American Fertility Society (AFS) scores for the 242 patients who were randomized to the LD or LD/N treatment groups in both studies are presented in Table 9. There were no statistically significant differences between the treatment groups with respect to time since the diagnosis of endometriosis or the percentage of patients with a prior pregnancy. The mean endometrial implant scores for the LD and LD/N groups (6.4 and 6.0) were similar in Study M92-878 and numerically lower than that in Study M97-777. The mean total AFS score (the sum of the endometrial implant and adhesion scores) was lower in the LD/N group (9.8) in Study M92-878 than in either of the other 2 treatment groups (15.7 and 18.4, respectively). The differences, however, were not statistically significant. A higher percentage of patients in the LD treatment group (39%) had a history of prior GnRH use than in either of the LD/N treatment groups (18% and 21 %, respectively).

**Medical Officer's Comment**

- *AFS scores are based on the extent of endometriosis as assessed at the time of laparoscopy or laparotomy. There is not a strong correlation between the AFS score and the severity of the patient's painful symptoms of endometriosis (the endometriosis clinical pain scores) that were used to assess the efficacy of treatment with either LD or LD/N. Mean baseline endometriosis clinical pain scores (see Table 13 and Table 14) were similar in all treatment groups.*

**Table 9 Disease and Fertility History**

| | Study M92-878 | | | | Study M97-777 | |
|---|---|---|---|---|---|---|
| | LD-Only N=51 | | LD/N N=55 | | LD/N N=136 | |
| Parameter | N | (%) | N | (%) | N | (%) |
| Time since diagnosis | | | | | | |
| <1 yr | 26 | (51) | 29 | (53) | 64 | (47) |
| 1 yr to <3 yrs | 10 | (20) | 11 | (20) | 22 | (16) |
| 3 yrs to <5 yrs | 7 | (14) | 5 | (9) | 21 | (15) |
| ≥5 yrs | 8 | (16) | 10 | (18) | 29 | (21) |
| Mean (yrs) | 2.2 | | 2.6 | | 3.1 | |
| Prior pregnancy | 28 | (55) | 24 | (44) | 85 | (63) |
| Prior treatment for endometriosis | 42 | (82) | 49 | (89) | 114 | (84) |
| Prior GnRH analog usage | 20 | (39) | 10 | (18) [1] | 29 | (21) [1] |
| Mean AFS scores [2] | | | | | | |
| Endometriosis Implants | 6.4 | | 6.0 | | 9.4 | |
| Total Score [3] | 15.7 | | 9.8 | | 18.4 | |

[1] Statistically significantly different from LD-Only group ($p < 0.05$).
[2] AFS = American Fertility Society.
[3] Total score based on the sum of the endometriosis implant and adhesion scores.
Source: Text Table 3.2b, pg. 47 (ISE).

### 8.5.1.2 Disposition of Subjects

In Study M92-878, 51 and 55 patients were randomized to the LD and LD/N treatment groups, respectively. Of these patients, 42 of 51 LD patients (82%) and 42 of 55 LD/N patients (76%) completed 6 months (24 weeks) of treatment (Table 10). Thirty-two (32) of the 51 LD patients (63%) and 31 of the 55 LD/N patients (56%) completed the full 1-year (52-week) treatment period. In Study M97-777, 136 patients were enrolled into the LD/N treatment group. Of these, 103 patients (76%) and 82 patients (60%) completed 6 months and 1 year of treatment. Thirty nine (39) of 51 LD patients (76%) and 39 of 55 LD/N patients (71%) in Study M92-878 entered the first year of the 2 year follow-up period. Fourteen (14) of the 39 LD patients (36%) and 10 of the 39 LD/N patients (26%) completed 1 year of follow-up. In Study M77-777, 119 of 136 patients (88%) entered the 1-year follow-up period. Sixty-four (64) of the 119 patients (54%) completed follow-up.

**Table 10 Disposition of Patients**

| Outcome | Study M92-878 | | | | Study M97-777 | |
|---|---|---|---|---|---|---|
| | LD-Only | | LD/N | | LD/N | |
| | N | (%) | N | (%) | N | (%) |
| Randomized | 51 | | 55 | | 136 | |
| Completed 24 Weeks Treatment | 42 | (82)[+] | 42 | (76)[+] | 103 | (76)[+] |
| Completed Full Treatment (52 Weeks) | 32 | (63)[+] | 31 | (56)[+] | 82 | (60)[+] |
| Entered Follow up Year 1[●] | 39 | (76)[+] | 39 | (71)[+] | 119 | (88)[+] |
| Completed Follow-up Year 1 | 14 | (36)[$] | 10 | (26)[$] | 64 | (54)[$] |
| Entered Follow-up Year 2 | 18 | (35)[+] | 13 | (24)[+] | NA | NA[4] |
| Completed Follow-up Year 2 | 4 | (22)[$] | 6 | (46)[$] | NA | NA |

[●] Patients did not have to complete the Treatment Period in order to enter the Follow-up Period
[+] Based on the percentage of patients randomized.
[$] Based on the percentage of patients who entered the follow up period.
[4] NA – Year 2 of the Follow-up Period is not applicable to Study M97-777.
Source: Text Table 3.1a, pg. 48 (ISS) and Statistical Report of FDA Statistician.

**Medical Officer's Comment**

- *The percentages of patients who completed treatment in each of the 3 treatment groups were very similar, suggesting that the addition of NETA neither increased nor decreased the overall acceptability of Lupron therapy.*

### 8.5.1.3 Number of Days in Treatment and Follow-up Periods

Thirty-two (32) of 51 patients (63%) enrolled into the LD treatment group and 31 of 55 patients (56%) enrolled into the LD/N treatment group received all 13 injections of Lupron in Study M92-878. In Study M97-777, 83 of 136 LD/N patients (61%) received all 13 injections. Table 11 summarizes the median and range for the number of days in the Treatment and Follow-up Periods. The median number of days of Lupron treatment for each group was as follows: LD-group in Study M92-878, 366 days; LD/N group in Study M92-878, 365 days, and LD/N group in Study M97-777, 364 days.

**Table 11 Number of Days in Treatment and Follow-up Periods**

| Study Period | | Study M92-878 | | Study M97-777 |
|---|---|---|---|---|
| | | LD-Only | LD/N | LD/N |
| Treatment Period | No. Patients | N=51 | N=55 | N=136 |
| | Median (days) | 366 | 365 | 364 |
| | Range (days) | 29–456 | 29–420 | 29–410 |
| Follow-up Period | No. Patients | N=39 | N=39 | N=119 |
| | Median | 329 | 245 | 362 |
| | Range | 7–736 | 5–786 | 7-473 |

Source: Text Table 3.1a, pg. 49 (ISS).

**Medical Officer's Comment**

- *Based on the upper values for the ranges of the treatment periods, it appears that one or more patients in each treatment group may have received more than 13 doses of Lupron.*

### 8.5.2 Primary Efficacy Assessments and Endpoints

#### 8.5.2.1 Treatment Period

The proportion (%) of patients with symptoms of endometriosis at baseline, Treatment Weeks 24 and 48, and the final treatment visit in each of the 3 treatment groups are listed in Table 12. The proportion (%) of patients with painful symptoms was numerically lower at each of these on-treatment assessment times compared to baseline.

**Table 12 Proportion of Patients with Symptoms of Endometriosis at Baseline, Treatment Weeks 24 and 48, and Final Treatment Visit (Studies M92-878 and M97-777)**

| | | | Baseline | | Week 24 | | Week 48 | | Final Visit | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Study | Group | N [1] | (%) [2] | N | (%) | N | (%) | N | (%) |
| Dysmenorrhea | M92-878 | LD | 51 | (100) | 37 | (3) | 31 | (0) | 50 | (4) |
| | | LD/N | 55 | (100) | 38 | (3) | 30 | (0) | 54 | (4) |
| | M97-777 | LD/N | 136 | (99) | 104 | (5) | 80 | (0) | 134 | (9) |
| Pelvic Pain | M92-878 | LD | 51 | (100) | 37 | (76) | 31 | (48) | 50 | (66) |
| | | LD/N | 55 | (96) | 38 | (66) | 30 | (50) | 54 | (56) |
| | M97-777 | LD/N | 136 | (99) | 105 | (69) | 80 | (55) | 134 | (63) |
| Deep Dyspareunia | M92-878 | LD | 42 | (83) | 29 | (38) | 24 | (33) | 46 | (37) |
| | | LD/N | 43 | (84) | 27 | (41) | 19 | (26) | 42 | (45) |
| | M97-777 | LD/N | 102 | (91) | 74 | (61) | 54 | (54) | 111 | (53) |
| Pelvic Tenderness | M92-878 | LD | 51 | (94) | 35 | (49) | 30 | (33) | 50 | (34) |
| | | LD/N | 54 | (91) | 37 | (24) | 30 | (23) | 53 | (34) |
| | M97-777 | LD/N | 136 | (99) | 105 | (39) | 79 | (32) | 134 | (39) |
| Pelvic Induration | M92-878 | LD | 51 | (51) | 35 | (11) | 30 | (13) | 50 | (12) |
| | | LD/N | 54 | (46) | 37 | (19) | 30 | (17) | 53 | (17) |
| | M97-777 | LD/N | 136 | (75) | 105 | (29) | 79 | (22) | 134 | (21) |

[1] Number of patients evaluated for the symptom/sign.
[2] Percent of patients evaluated who reported the symptom/sign.
Source: Statistical Tables 1.11 and 2.11 of ISE.

**Medical Officer's Comments**

- *There were no consistent numerical differences in the reduction in the proportion of patients with painful symptoms/signs of endometriosis between the LD and the LD/N treatment groups in Study M92-878.*
- *The percentages of patients with dyspareunia and pelvic induration were numerically larger in Study M97-777. These differences tended to persistent in the treatment period.*
- *In Table 12 and other efficacy tables in which represented data were obtained at monthly visits, the data presented or summarized in a specific column generally includes only data obtained within ±2 weeks of the column label. For bone mineral density and general laboratory safety data the intervals were generally much broader (see Section 9.9.1 and the footer to Table 37).*
- *In most efficacy tables, Week 48 data, instead of Week 52, data are shown. The decision to present Week 48 data was made because the number of patients evaluated at Week 52 for some assessments appeared to be considerably smaller than at Week 48.*

Mean clinical pain scores at baseline and the changes from baseline at Study Weeks 24 and 48 and the Final Treatment Visit for both treatment groups in Study M92-878 are listed in Table 13. Also

listed in Table 13 are the average changes in clinical pain scores throughout the treatment period. There were no statistically significant differences between the LD and LD/N treatment groups in mean pain scores at baseline with the exception of pelvic induration ($p = 0.050$), where the mean score for the LD group was greater than that of the LD/N group. Statistically significant decreases from baseline values (clinical improvement) for all parameters at each of the assessment times listed in Table 13 were observed in both the LD and LD/N treatment groups. The improvements were generally statistically significant by Week 4 and were maintained throughout the Treatment Period.

**Table 13 Clinical Pain Scores: Changes from Baseline Values during Treatment with LD or LD/N (Study M92-878)**

| Variable | Group | N | Baseline Mean | Average Change* | Final Change* | Week 24 | | Week 48 | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | N | Change* | N | Change* |
| Dysmenorrhea | LD | 50 | 3.2 | -1.9 | -2.0 | 36 | -2.0 | 28 | -2.1 |
| | LD/N | 54 | 3.1 | -1.9 | -2.0 | 33 | -2.1 | 26 | -2.1 |
| Pelvic Pain | LD | 50 | 2.9 | -0.9 | -1.1 | 36 | -1.1 | 28 | -1.5 |
| | LD/N | 54 | 3.1 | -0.8 | -1.1 | 33 | -1.1 | 26 | -1.5 |
| Deep Dyspareunia | LD | 25 | 2.4 | -0.6 | -1.0 | 10 | -1.0 | 8 | -1.0 |
| | LD/N | 30 | 2.7 | -0.8 | -0.8 | 12 | -0.8 | 7 | -1.1 |
| Pelvic Tenderness | LD | 50 | 2.5 | -0.8 | -1.0 | 33 | -0.9 | 27 | -1.0 |
| | LD/N | 52 | 2.6 | -0.8 | -0.9 | 32 | -1.2 | 26 | -1.3 |
| Pelvic Induration | LD | 50 | 1.9+ | -0.4 | -0.4 | 33 | -0.5 | 27 | -0.5 |
| | LD/N | 52 | 1.6 | -0.4 | -0.4 | 32 | -0.3 | 26 | -0.4 |

* Statistically significantly different from LD/N group.
* Statistically significant within-group decreases from baseline for all symptoms/signs.
Source: Statistical Table 1.15 of ISE.

**Medical Officer's Comment**

- *In general, there were no significant differences between the two treatment groups in mean changes from baseline at any of the treatment visits for any of the pain scores. There also were no statistically significant differences between the two treatment groups in the changes from baseline averaged over the Treatment Period for any of the pain scores.*

Mean clinical pain scores at baseline and the changes from baseline at Study Weeks 24 and 48 and the Final Treatment Visit for patients in Study M97-777 are listed in Table 14. Statistically significant decreases from baseline (i.e., improvements) in all clinical pain scores generally occurred by Week 4 and were maintained throughout the Treatment Period. The mean changes from baseline averaged over the Treatment Period also were statistically significant for all of the clinical pain parameters.

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**Table 14 Clinical Pain Scores: Changes from Baseline Values during Treatment with LD/N (Study M97-777)**

| Variable | Group | N | Baseline Mean | Average Change* | Final Change* | Week 24 | | Week 48 | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | N | Change* | N | Change* |
| Dysmenorrhea | LD/N | 134 | 3.3 | -2.0 | -2.1 | 104 | -2.2 | 80 | -2.2 |
| Pelvic Pain | LD/N | 134 | 3.2 | -1.1 | -1.2 | 105 | -1.2 | 80 | -1.5 |
| Deep Dyspareunia | LD/N | 94 | 2.7 | -0.9 | -1.0 | 68 | -0.9 | 48 | -1.0 |
| Pelvic Tenderness | LD/N | 134 | 2.9 | -1.2 | -1.4 | 105 | -1.5 | 79 | -1.5 |
| Pelvic Induration | LD/N | 134 | 2.2 | -0.8 | -0.9 | 105 | -0.8 | 79 | -0.9 |

* Statistically significant within-group decreases from baseline for all symptoms/signs.
Source: Statistical Table 2.15 of ISE.

## Medical Officer's Comments

- *Comparison of the findings in Study M97-777 to those in M92-878 must be interpreted with caution, particularly since M97-777 was an open label study and efficacy assessments in both were subjective. Based on the data represented in Table 13 and Table 14, however, there are no findings that suggest that treatment with LD/N in Study M97-777 was less effective than treatment with LD alone in Study M92-878.*
- *At the request of the Medical Officer, the FDA statistician summarized the efficacy results for Study M92-878 in terms of the percent of subjects who had clinical improvement at their final Treatment Visit (Table 15). The between-group differences and the 2-sided 95% confidence intervals (CIs) for the differences are also listed. The differences between the LD and LD/N treatment groups (i.e., LD-LD/N) were relatively small and ranged from –4% to +9%. However, the 95% CIs were wide due to the relatively small sample size.*
- *The outcome of the analysis summarized in Table 15 is consistent with the Sponsor's efficacy analyses in that it did not show a difference in the efficacy of LD/N compared to that of LD alone.*

**Table 15 Percent of Patients with Symptom at Baseline Who Improved at their Final Treatment Visit Based on Clinical Pain Scores (Study M92-878)**

| | LD Group | | | LD/N Group | | | Between Group Comparison** | |
|---|---|---|---|---|---|---|---|---|
| Primary Efficacy Variables | N [1] | # improved/ # with symptom at baseline | % Improved | N [1] | # improved/ # with symptoms at baseline | % Improved | Difference (LD – LD/N) | 95% 2-sided CI on Difference |
| Dysmenorrhea | 50 | 48/50 | 96% | 54 | 54/54 | 100% | -4% | (-9%, 1%) |
| Pelvic Pain | 50 | 33/50 | 66% | 54 | 38/52 | 73% | -7% | (-25%, 11%) |
| Dyspareunia | 40 | 24/34 | 71% | 42 | 25/35 | 71% | 0% | (-22%, 21%) |
| Tenderness | 50 | 35/47 | 75% | 52 | 40/48 | 83% | -8% | (-25%, 8%) |
| Pelvic Induration | 50 | 22/25 | 88% | 52 | 19/24 | 79% | +9% | (-12%, 30%) |

[1] Number of patients assessed for the efficacy variable at baseline.
Source: Table 6 of FDA Statistical Review.

### 8.5.2.2 Post Treatment Period

Efficacy assessments and endpoints in the posttreatment Follow-up Period included the time (i.e., number of months) until the patient's painful symptoms/signs of endometriosis had returned to baseline severity. Separate analyses were performed based on (1) all patients who were treated with each Study Drug (ITT population) and (2) only those patients considered to have successfully completed the Treatment Period (i.e., those who received all 13 injections of Lupron). Changes from baseline clinical pain scores at follow-up visits, another assessment of the persistence of therapeutic benefit, also were calculated and summarized by the Sponsor. These latter analyses included only data from patients who had successfully completed the Treatment Period.

Table 16 lists the mean and median post treatment times until each of the symptoms/signs of endometriosis had returned to baseline severity (duration of therapeutic improvement measured in months). Among all patients in Study M92-878, mean posttreatment improvement times ranged from 5.4 months (pelvic tenderness, LD group) to 9.2 months (pelvic induration, LD group). Among successful completers in Study M92-878, mean posttreatment improvement times ranged from 6.8 months (dysmenorrhea, LD/N group) to 13.0 months (pelvic induration, LD group). The durations of therapeutic improvement in the LD/N patients in Study M97-777 were similar to those in Study M92-878.

**Table 16 Time (Months) to Return to Baseline Pain Severity - Clinical Pain Evaluations**

| Variable | Study | Treatment Group | All Patients | | | Successful Completers | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Mean | Median | N | Mean | Median |
| Dysmenorrhea | M92-878 | LD | 50 | 7.1 | 4.0 | 31 | 8.6 | 8.0 |
| | | LD/N | 54 | 6.4 | 4.0 | 31 | 6.8 | 4.0 |
| | M97-777[1] | LD/N | 133 | 7.5 | 4.0 | 88 | 8.9 | 8.0 |
| Pelvic Pain | M92-878 | LD | 50 | 6.1 | 3.0 | 23 | 9.5 | 8.0 |
| | | LD/N | 52 | 7.0 | 8.0 | 27 | 10.0 | 12.0 |
| | M97-777 | LD/N | 133 | 7.3 | 4.0 | 77 | 9.8 | 12.0 |
| Deep Dyspareunia | M92-878 | LD | 34 | 6.4 | 1.0 | 15 | 10.5 | 12.0 |
| | | LD/N | 36 | 6.0 | 2.0 | 16 | 9.9 | 12.0 |
| | M97-777 | LD/N | 87 | 8.4 | 12.0 | 47 | 12.6 | 16.0[1] |
| Pelvic Tenderness | M92-878 | LD | 47 | 5.4 | 2.0 | 23 | 8.7 | 8.0 |
| | | LD/N | 48 | 7.7 | 8.0 | 27 | 9.3 | 12.0 |
| | M97-777 | LD/N | 133 | 8.8 | 8.0 | 85 | 10.9 | 16.0[1] |
| Pelvic Induration | M92-878 | LD | 27 | 9.2 | 12.0 | 15 | 13.0 | 16.0 |
| | | LD/N | 26 | 6.9 | 8.0 | 13 | 10.0 | 8.0 |
| | M97-777 | LD/N | 101 | 9.8 | 16.0[1] | 60 | 12.6 | 16.0[1] |

[1] Patients censored at 12 months (follow-up period was 12 months in Study M97-777) were assigned a value of 16 months for calculation of mean and median values.

Source: Statistical Tables 1.17 and 1.18 and Appendices A.1 and A.2 for Study M92-878.
Source: Statistical Tables 14.2__1.1.1 and 14.2__1.1.2 and Appendices 16.2__6.1.1 and 16.2__6.1.2.1 for Study M97-777.

**Medical Officer's Comment**

*There were no consistent differences in the mean durations of therapeutic improvement between the LD and LD/N treatment groups among either all patients or successful completers in Study M92-878.*

Table 17 lists the mean changes from baseline at Post Treatment Month 12 for each of the symptoms/signs of endometriosis assessed by 4-point severity scores in the ITT population. In Study M92-878, all categories were statistically different from baseline at Month 12 and the changes were all in the direction of clinical improvement (i.e., the changes in the severity scores were negative).

The mean changes in severity scores at post treatment Month 12 (improvement from baseline) ranged from –0.6 (dysmenorrhea in the LD group) to –1.3 (pelvic tenderness in the LD/N group).

The mean changes in the severity of signs/symptoms of endometriosis at post treatment Month 12 in the LD/N patients in Study M97-777 were similar to those in Study M92-878.

**Table 17 Mean Changes in Clinical Pain – Baseline versus Month 12 of Follow-up**

| Variable | Study | Treatment Group | Intent-to-Treat Population | | |
|---|---|---|---|---|---|
| | | | N | Baseline Mean | Month 12 Mean Change |
| Dysmenorrhea | M92-878 | LD | 29 | 3.1 | -0.6* |
| | | LD/N | 29 | 3.0 | -0.7* |
| | M97-777 | LD/N | 82 | 3.2 | -1.0* |
| Pelvic Pain | M92-878 | LD | 22 | 3.2 | -1.2* |
| | | LD/N | 26 | 3.3 | -1.0* |
| | M97-777 | LD/N | 72 | 3.3 | -1.3* |
| Deep Dyspareunia | M92-878 | LD | 15 | 2.7 | -1.2* |
| | | LD/N | 15 | 2.7 | -0.9* |
| | M97-777 | LD/N | 42 | 3.0 | -1.2* |
| Pelvic Tenderness | M92-878 | LD | 22 | 2.6 | -1.0* |
| | | LD/N | 25 | 2.8 | -1.3* |
| | M97-777 | LD/N | 78 | 2.9 | -1.4* |
| Pelvic Induration | M92-878 | LD | 14 | 2.4 | -1.1* |
| | | LD/N | 12 | 2.3 | -0.7* |
| | M97-777 | LD/N | 55 | 2.6 | -1.3* |

* Statistically significant within-group decrease from baseline
Source: Statistical Tables 1.19, 1.20 for Study M92-878 and Statistical Tables 14.2__1.2.1 and 14.2__1.3.1 and Appendices 16.2__6.1.1 and 16.2__6.1.2.1 for Study M97-777.

**Medical Officer's Comment**

- *There were no consistent differences in the mean changes (degree of therapeutic improvement) between the LD and LD/N treatment groups in Study M92-878 at posttreatment Month 12. The decreases at Month 12 tended to be numerically greater in Study M97-777.*

### 8.5.2.3 Patients Previously Treated with a GnRH Analog for Endometriosis

The original submission did not specifically assess the clinical response to treatment with LD or LD/N in patients previous treated with a GnRH analog. Since the requested labeling change included removing the restriction against retreatment, the Sponsor was requested to provide a subset analysis comparing clinical responses in patients previously treated with a GnRH analog to those in patients not previously treated. The analysis was limited to patients treated with LD/N in Studies M92-878 and M97-777 because retreatment with LD alone is not under consideration. Forty (40) patients had previously been treated with a GnRH analog (10 in Study M92-878 and 30 in M97-777). Among these patients, the mean (SD) and median duration of prior GnRH treatment was 178.0 (133.12) and 151.0 days (range: 1-667 days).

The proportion (%) of patients with symptoms of endometriosis at baseline, Treatment Weeks 24 and 48, and the Final Treatment Visit in this subset analysis are listed in Table 18. The proportion of patients with each of the symptoms/signs of endometriosis at baseline was similar in the 2 subgroups. The proportion (%) of patients with symptoms was numerically lower at each of the on-treatment assessment times in both subgroups.

**Table 18 Proportion (%) of Patients with Symptoms of Endometriosis after Treatment with LD/N (Patients with or without Prior GnRH Treatment)**

| Variable | Group | Baseline* N | Baseline* (%) | Week 24* N | Week 24* (%) | Week 48* N | Week 48* (%) | Final Visit* N | Final Visit* (%) |
|---|---|---|---|---|---|---|---|---|---|
| Dysmenorrhea | Prior GnRH [1] | 40 | (100) | 28 | (0) | 26 | (0) | 39 | (3) |
| | No GnRH [2] | 151 | (99) | 114 | (5) | 84 | (0) | 149 | (9) |
| Pelvic Pain | Prior GnRH | 40 | (98) | 28 | (71) | 26 | (65) | 39 | (69) |
| | No GnRH | 151 | (99) | 115 | (67) | 84 | (60) | 149 | (59) |
| Deep Dyspareunia | Prior GnRH | 28 | (86) | 17 | (53) | 13 | (54) | 26 | (50) |
| | No GnRH | 117 | (90) | 84 | (56) | 60 | (45) | 127 | (51) |
| Pelvic Tenderness | Prior GnRH | 40 | (93) | 27 | (44) | 26 | (27) | 38 | (34) |
| | No GnRH | 150 | (98) | 115 | (33) | 83 | (30) | 149 | (38) |
| Pelvic Induration | Prior GnRH | 40 | (65) | 27 | (26) | 26 | (15) | 38 | (16) |
| | No GnRH | 150 | (67) | 115 | (26) | 83 | (22) | 149 | (21) |

* Combined data from LD/N treatment groups in Studies M92-878 and M97-777.
[1] Prior GnRH = Patients previously treated with a GnRH analog for endometriosis.
[2] No GnRH = Patients not previously treated with a GnRH analog for endometriosis.
Source: Statistical Table 4.2.1.1, Submission of August 10, 2001.

## Medical Officer's Comment

- *There were no consistent numerical differences in the proportion of patients with painful symptoms of endometriosis during treatment with Lupron plus NETA across the prior-GnRH treatment group and the no-prior-GnRH treatment group.*

Mean clinical pain scores at baseline and the changes from baseline at Study Weeks 24 and 48 and the Final Treatment Visit for both subgroups are listed in Table 19. Also listed in Table 19 are average changes in clinical pain scores throughout the treatment period. There were no significant differences between the 2 groups in mean pain scores at baseline for any of the clinical assessments. Statistically significant decreases from baseline values (clinical improvement) were observed in both groups of patients for all parameters at each of the assessment times listed in Table 19.

**Table 19 Clinical Pain Severity Scores: Changes from Baseline Values during Treatment with LD/N (Patients with or without Prior GnRH Treatment)**

| Variable | Group [1] | N | Baseline Mean | Average Change* | Final Change* | Week 24 N | Week 24 Change* | Week 48 N | Week 48 Change* |
|---|---|---|---|---|---|---|---|---|---|
| Dysmenorrhea | Prior GnRH [2] | 39 | 3.1 | -2.1 | -2.2 | 28 | -2.2 | 26 | -2.2 |
| | No GnRH [3] | 149 | 3.2 | -2.0 | -2.1 | 114 | -2.1 | 84 | -2.2 |
| Pelvic Pain | Prior GnRH | 39 | 3.0 | -1.0 | -1.2 | 28 | -1.2 | 26 | -1.3 |
| | No GnRH | 149 | 3.2 | -1.1 | -1.2 | 115 | -1.2 | 84 | -1.5 |
| Deep Dyspareunia | Prior GnRH | 24 | 2.5 | -0.9 | -0.9 | 16 | -0.9 | 12 | -1.1 |
| | No GnRH | 112 | 2.7 | -0.8 | -0.9 | 79 | -0.9 | 55 | -1.0 |
| Pelvic Tenderness | Prior GnRH | 38 | 2.8 | -1.1 | -1.4 | 27 | -1.3 | 26 | -1.5 |
| | No GnRH | 148 | 2.8 | -1.1 | -1.3 | 115 | -1.4 | 83 | -1.5 |
| Pelvic Induration | Prior GnRH | 38 | 2.0 | -0.6 | -0.8 | 27 | -0.7 | 26 | -0.8 |
| | No GnRH | 148 | 2.0 | -0.6 | -0.8 | 115 | -0.7 | 83 | -0.7 |

[1] Data are combined from LD/N treatment groups in Studies M92-878 and M97-777
[2] Prior GnRH = Patients previously treated with a GnRH analog for endometriosis.
[3] No GnRH = Patients not previously treated with a GnRH analog for endometriosis.
* Statistically significant decreases from baseline for all variables.
Source: Statistical Table 4.2.1.2, Submission of August 10, 2001.

**Medical Officer's Comments**

- *There were no significant numerical differences between the two groups in terms of mean changes from baseline (improvement in symptoms) at Treatment Weeks 24 or 48, at the Final Treatment Visit, or in the average change from baseline for any of the clinical pain scores.*
- *An analysis by the Sponsor (ANOVA) did not show any consistent statistical differences between the clinical responses of the 2 subsets of patients. The small sample size, however, limits the value of the analysis because the statistical power to show a difference was low. However, the numerical data by themselves suggest that retreatment is as effective as primary treatment in relieving painful symptoms of endometriosis in that there were no trends across the 5 assessments of pain in favor of the patients who had not been treated previously with a GnRH analog.*

### 8.5.3 Secondary Efficacy Assessments

#### 8.5.3.1 Reduction in Serum Estradiol Concentrations

During the treatment period, serum estradiol levels were determined at each protocol scheduled visit. In Study M92-878, the mean serum estradiol levels at baseline were 58.1 pg/mL and 50.5 pg/mL in the LD and LD/N groups, respectively (see Table 20). Statistically significant within-group mean decreases from baseline were noted for both groups at each visit during the Treatment Period. The mean serum estradiol level averaged over the Treatment Period was within the menopausal range (≤ 20 pg/mL) for both treatment groups: 14.5 pg/mL for the LD group and 8.6 pg/mL for LD/N group. In Study M97-777, the mean serum estradiol level for the LD/N group was 48.4 pg/mL at baseline and 8.4 pg/mL averaged over the treatment period.

**Table 20 Serum Estradiol Concentrations at Baseline and during the Treatment Period**

| Treatment Group | Study | Number Patients | Estradiol (pg/mL) | |
|---|---|---|---|---|
| | | | Baseline | Treatment [1] |
| LD | M92-878 | 45 | 58.1 | 14.5 |
| LD/N | M92-878 | 45 | 50.5 | 8.6 |
| LD/N | M97-777 | 133 | 48.4 | 8.4 |

[1] Average estradiol concentration during the treatment period
Source: Statistical Tables 1.33 and 2.23 of ISE.

**Medical Officer's Comment**

- *Treatment with LD/N suppressed total serum estradiol concentrations to a statistically significant greater degree than LD alone. In both studies the Sponsor reported only total serum estradiol levels and did not measure serum levels of sex hormone binding globulin (SHBG) or free (biologically active) estradiol. Norethindrone acetate and other androgenic progestins are known to reduce serum concentrations of SHBG. Since approximately 50% of estradiol in serum is bound to SHBG and is therefore not biologically active, it is not known if biologically active levels of estradiol differed in the LD-treated and LD/N-treated patients.*

#### 8.5.3.2 Suppression of Menses

Menstrual bleeding during the prior 28-day interval was summarized at each clinical visit during the treatment period based on the patient's daily diary. Menses was defined as bleeding for 3 or more consecutive days requiring the use of sanitary products. Suppression of menses was defined to be no menses for at least 60 consecutive days during treatment, regardless of whether any bleeding occurred thereafter. Time to suppression was defined as the number of days from the start of treatment to the first day of the last menstrual cycle prior to suppression. Patients who had no bleeding for at least 60 days after the start of study medication were defined as having zero days to suppression. A

summary of menstrual bleeding data for patients who were in the Treatment Period for at least 60 days is presented in Table 21. The percentages of patients who ceased to have menstrual bleeding and who experienced no further menstrual bleeding through the end of treatment were 87% and 84% in the LD and LD/N groups, respectively, in Study M92-878 and 73% in the LD/N group in Study M97-777.

**Table 21 Menses Suppression during the Treatment Period**

| | Study M92-878 | | Study M97-777 |
|---|---|---|---|
| Parameter | LD | LD/N | LD/N |
| Percent of Patients with Suppression N (%) | 47/47 (100) | 50/50 (100) | 124/127 (98) |
| Time to Suppression (Days) | | | |
| Median | 0 | 0 | 0 |
| Range | 0–146 | 0–73 | 0–115 |
| Suppression Maintained to End of Treatment N (%) | 41/47 (87) | 42/50 (84) | 90/124 (73) |

Reference: Text Table 3.8a, pg. 78 of ISE

**Medical Officer's Comments**

- *The Sponsor's definitions for both "suppression of menses" and "maintenance of suppression" were not very stringent. A patient was required to have menstrual bleeding for 3 or more consecutive days before being classified as a failure in terms of suppression of menses.*
- *A third secondary efficacy evaluation was the "patient assessment of pain." Data related to this assessment (in contrast to the primary efficacy assessment of "clinical assessment of pain") were not reviewed by the Medical Officer. The sponsor stated that the relative efficacy of treatment with LD or LD/N based on this secondary assessment was similar to that reported for the primary efficacy assessment.*

## 8.6 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoint)

The FDA Statistician (Ms. K. Meaker) reviewed and confirmed the Sponsor's primary efficacy and safety analyses. Her review did not raise any serious concerns regarding the Sponsor's analyses. Many of the limitations identified by the FDA Statistician regarding the Sponsor's interpretation of these analyses also were noted by the Medical Reviewer and have been incorporated in the Medical Officer's Comments throughout this review.

## 8.7 Medical Officer's Overall Assessment of Demonstrated Efficacy

### 8.7.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

**Reduction in Painful Symptoms and Signs of Endometriosis.**

The primary objective of these supplemental NDAs was a safety endpoint, namely, to demonstrate that treatment with Lupron plus NETA significantly reduced the decrease in bone mineral density that is observed following treatment with Lupron alone. Study M92-878 was a well-designed, randomized, controlled clinical trial, but it was not powered or intended to show statistical equivalence or non-inferiority of Lupron plus NETA compared to Lupron alone in terms of reduction of the symptoms and signs of endometriosis. The planned sample size of 50 patients per treatment group, according to the Sponsor, would provide 80% power to detect a difference between the treatment groups if the true mean of the difference in severity score were at least 0.51. Since the mean decreases from baseline for the clinical pain severity scores (other than dysmenorrhea) did not

exceed 1.5 pain units, the absence of statistical differences should not be interpreted as demonstrating statistical non-inferiority.

Although the small sample size of Study M92-878 and the unblinded, noncomparative design of Study M97-777 limited the statistical assessment of the comparative efficacy of the 2 treatments, the responses to treatment were similar, based on (1) the numerical changes in the 5 clinical pain severity scores and (2) the changes in the proportion of patients with symptoms and signs of endometriosis after 6 and 12 months of treatment. A supplemental analysis requested by the Medical Reviewer of the efficacy data from Study M92-878 supported the Sponsor's claim. In this analysis, the differences between the 2 treatment groups in terms of the percentages of patients who had clinical improvement at their final Treatment Visit was small and ranged [redacted] However, the 95% CIs were wide due to the relatively small sample size.

The original submission did not specifically assess the clinical response to treatment with LD or LD/N in patients previous treated with a GnRH analog. Since the requested labeling change included removing the restriction against retreatment, the Sponsor was requested to provide a subset analysis comparing clinical responses in patients previously treated with a GnRH analog to those in patients not previously treated. The analysis was limited to patients treated with LD/N in Studies M92-878 and M97-777 because retreatment with LD alone is not under consideration. Forty (40) patients had previously been treated with a GnRH analog (10 in Study M92-878 and 30 in M97-777). The responses to treatment in the two groups were similar, based on (1) the mean changes from baseline (improvement in symptoms) and (2) the decrease in the proportion of patients with painful symptoms of endometriosis.

### 8.7.2 Support of Label Efficacy Claim

Based on the findings in Studies M92-878 and M97-777, revised labeling for Lupron Depot can include a statement that co-treatment with 5 mg norethindrone acetate did not appear to reduce the efficacy of Lupron as assessed by the modified grading system of [redacted]

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# 9 INTEGRATED REVIEW OF SAFETY

## 9.1 Extent of Exposure to Study Drugs

In Study M92-878, 32 of 51 patients (63%) randomized into the LD-treatment group and 31 of 55 patients (56%) randomized into the LD/N treatment group received all 13 injections. In Study M97-777, 82 of 136 (60%) patients received all 13 injections. The extent of exposure to Lupron, which was comparable for each treatment group, is presented in Table 22.

**Table 22 Extent of Lupron Exposure (% of Patients)**

| Number of Days | Study M92-878 LD (N= 51) | Study M92-878 LD/N (N =55) | Study M97-777 LD/N (N = 136) |
|---|---|---|---|
| >29 | 96 | 98 | 97 |
| >59 | 92 | 91 | 93 |
| >89 | 86 | 84 | 89 |
| >119 | 86 | 82 | 83 |
| >149 | 84 | 76 | 81 |
| >179 | 78 | 75 | 75 |
| >209 | 78 | 71 | 71 |
| >239 | 73 | 67 | 69 |
| >269 | 71 | 62 | 67 |
| >299 | 65 | 60 | 64 |
| >329 | 65 | 56 | 62 |
| >359 | 63 | 56 | 60 |

Source: Text Table 3.3a of ISS.

**Medical Officer's Comment**

- *Both Lupron Depot and Aygestin (NETA) are approved therapies for endometriosis with well known safety profiles. The number of patients treated with Lupron plus NETA and the duration of treatment in Studies M92-878 and M97-777 were sufficient to assess the safety of the combination therapy in the intended population.*

Compliance with daily oral dosing was determined by the study coordinators at each visit via a count of capsules (Study M92-878) or tablets (Study M97-777) from returned bottles. A patient was deemed compliant at a particular study visit if she took 80% to 120%, inclusive, of the prescribed capsules or tablets during the four weeks between visits. The percent of compliant visits for norethindrone acetate 5 mg (Aygestin®) or placebo is presented in Table 23. Patients were assessed as being compliant with NETA dosing 93% (Study M92-878) and 94% (Study M97-777) of the time in the month preceding a clinical visit.

**Table 23 Norethindrone Acetate 5 mg (Aygestin®) Compliance**

| | Study M92-878 | | | | Study M97-777 | |
|---|---|---|---|---|---|---|
| | LD* | | LD/N | | LD/N | |
| Parameter | N | (%) | N | (%) | N | (%) |
| Compliant Visits | 476/520 | (92) | 499/534 | (93) | 1293/1374 | (94) |

*LD group received placebo capsules.
Source: Text Table 3.3d of ISS.

## 9.2 Protocol Defined Safety Assessments in the Primary Safety Study

### 9.2.1 Overview of Safety Evaluations

Safety assessments in both studies included collection of adverse events, bone mineral density measurements, general clinical laboratory evaluations, measurements of serum lipids, recording of vital signs and body weight, physical examinations, recording of concomitant medications, and endometrial biopsies (if clinically indicated). Figure 1and Figure 2 (pages 30 and 31) and Table 24 below present overviews of the schedule of safety evaluations that were performed.

**Table 24 Summary of Schedule of Safety Evaluations**

| Safety Evaluation | Prestudy and Treatment Period | Follow-up Period |
|---|---|---|
| Adverse Events | Prestudy, Day 0, and every 4 weeks through Week 52 | Every month through Month 4, then every 4 months through Month 12 |
| Vasomotor Symptoms [1] | Daily recording in patient diaries with data collection at Day 0 and every 4 weeks through Week 52 | Daily recording in patient diaries with data collection every month through Month 4, then Months 8 and 12 |
| Bone Mineral Density | Prestudy, Week 24, and Week 52 | Month 8 and 12 [2] |
| Clinical Laboratory Evaluations | Prestudy, Week 24, and Week 52. Urine pregnancy tests were performed prestudy (within 1 week prior to dosing) and prior to dosing at Week 4. | Lipid profiles only.<br>Study M92-878: every 4 months from Month 8 through Month 24.<br>Study M97-777: every month through Month 4, then every 4 months through Month 12. |
| Vital Signs and Body Weight | Prestudy, Week 24, and Week 52 | Not required per protocol |
| Physical Examination | Prestudy, Week 24, and Week 52 | Not required per protocol |
| Concomitant Medications | Prestudy, Day 0, and every 4 weeks through Week 52 | Every month through Month 4, then every 4 months through Month 12 |
| Endometrial Biopsy | Prestudy (M92-878 only) and only if clinically indicated thereafter (M92-878 and M97-777) | Not required per protocol |
| Serum Estradiol Levels | Treatment Period data considered efficacy data | At the initial visit after resumption of menses |
| Menses Resumption | <Not applicable> | Daily recording in patient diaries; data collected through the first post-treatment menstrual cycle |

[1] Vasomotor symptoms were assessed in Study M92-878 only.
[2] Study M92-878 allowed for additional assessments at posttreatment Months 16, 20, and 24.

### 9.2.2 Adverse Events

Adverse event data were obtained by patient report, patient diary, and questioning by the investigator, who rated the severity of the event and its likely relationship to Study Drug. Adverse event data were collected at each clinical visit (scheduled at 28-day intervals during the treatment period).

### 9.2.3 Clinical Laboratory Measurements

In both studies, patients were to fast overnight prior to collection of blood specimens for laboratory tests. Hematology and chemistry tests were performed during the pre-study period and at Weeks 24 and 52 of the Treatment Period. A baseline pregnancy test was performed within 1 week prior to the first administration of study drug and prior to Week 4 dosing to confirm that the patient was not pregnant. No laboratory measurements, other than serum lipid profiles, were required in the post